CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040236

Trade Name : HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS USP

Generic Name: Hydrocodone Bitartrate and Acetaminophen Tablets USP 5mg/500mg and 7.5mg/750mg

Sponsor : Halsey Drug Company, Inc.

Approval Date: September 25, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040236

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Medical Review(s)				
Chemistry Review(s)	X			
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Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
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Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040236

APPROVAL LETTER

ANDA 40-236

SEP 25 1997

Halsey Drug Company, Inc.
Attention: George F.J. Scholes
1827 Pacific St.
Brooklyn, NY 11233

Dear Mr. Scholes:

This is in reference to your abbreviated new drug application dated December 19, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg.

Reference is also made to your amendments dated May 5 and 7, 1997, August 8 and 28, 1997, and September 23, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Vicodin® 5 mg/500 mg tablets and Vicodin ES® 7.5 mg/750 mg tablets, respectively, of Knoll Pharmaceuticals Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040236

FINAL PRINTED LABELING

USUAL ADULT DOSAGE:
See package insert.

Store at controlled room temperature, 15°-30°C (59°-86°F).

HALSEY DRUG CO., INC.
Brooklyn, NY 11233 U.S.A.

NDC 0879-0765-01

HALSEY

HYDROCODONE* BITARTRATE and ACETAMINOPHEN TABLETS, USP

5 mg / 500 mg

Each tablet contains:
Hydrocodone* Bitartrate, USP ..... 5 mg
(***WARNING:** May be habit forming.)
Acetaminophen, USP ..... 500 mg

CAUTION: Federal law prohibits dispensing without prescription

100 TABLETS

SEP 25 1997

Dispense in a tight, light-resistant container with a child-resistant closure

0765 - 8/97

Lot No / Exp. See Container or Label

N 3 08790 76501 8

USUAL ADULT DOSAGE:
See package insert.

Store at controlled room temperature, 15°-30°C (59°-86°F).

HALSEY DRUG CO., INC.
Brooklyn, NY 11233 U.S.A.

NDC 0879-0765-01

HALSEY

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(***WARNING:** May be habit forming.)
Acetaminophen, USP ..... 500 mg

CAUTION: Federal law prohibits dispensing without prescription

100 TABLETS

SEP 25 1997

Dispense in a tight, light-resistant container with a child-resistant closure

0765 - 8/97

Lot No / Exp. See Container or Label

N 3 08790 76501 8

USUAL ADULT DOSAGE:
See package insert.

Store at controlled room temperature, 15°-30°C (59°-86°F).

HALSEY DRUG CO., INC.
Brooklyn, NY 11233 U.S.A.

NDC 0879-0765-10

HALSEY

C III

HYDROCODONE* BITARTRATE and ACETAMINOPHEN TABLETS, USP

5 mg / 500 mg

Each tablet contains:
Hydrocodone* Bitartrate, USP ..... 5 mg
(***WARNING:** May be habit forming.)
Acetaminophen, USP ..... 500 mg

CAUTION: Federal law prohibits dispensing without prescription

1000 TABLETS

SEP 25 1997

Dispense in a tight, light-resistant container with a child-resistant closure.

Lot No / Exp See Container or Label

0765 - 8/97

3 08790 76510 0

USUAL ADULT DOSAGE:
See package insert.

Store at controlled room temperature, 15°-30°C (59°-86°F).

HALSEY DRUG CO., INC.
Brooklyn, NY 11233 U.S.A.

NDC 0879-0765-10

HALSEY

C III

HYDROCODONE* BITARTRATE and ACETAMINOPHEN TABLETS, USP

5 mg / 500 mg

Each tablet contains:
Hydrocodone* Bitartrate, USP ..... 5 mg
(*WARNING: May be habit forming.)
Acetaminophen, USP ..... 500 mg

CAUTION: Federal law prohibits dispensing without prescription

1000 TABLETS

SEP 25 1997

Dispense in a tight, light-resistant container with a child-resistant closure.

Lot No / Exp See Container or Label

0765 - 8/97

3 08790 76510 0

USUAL ADULT DOSAGE:
See package insert.

Store at controlled room temperature, 15°-30°C (59°-86°F).

HALSEY DRUG CO., INC.
Brooklyn, NY 11233 U.S.A.

NDC 0879-0765-10

HALSEY

C III

HYDROCODONE* BITARTRATE and ACETAMINOPHEN TABLETS, USP

5 mg / 500 mg

Each tablet contains:
Hydrocodone* Bitartrate, USP ..... 5 mg
(*WARNING: May be habit forming.)
Acetaminophen, USP ..... 500 mg

CAUTION: Federal law prohibits dispensing without prescription

1000 TABLETS

SEP 25 1997

Dispense in a tight, light-resistant container with a child-resistant closure.

Lot No / Exp See Container or Label

0765 - 8/97

3 08790 76510 0

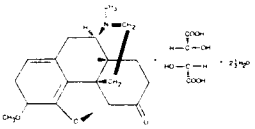
HYDROCODONE BITARTRATE & ACETAMINOPHEN TABLETS, USP 5mg/500mg

C-III

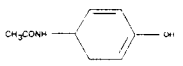
DESCRIPTION

Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. Its chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). The structural formula of hydrocodone bitartrate is shown at right. Its molecular weight is 494.50 and molecular formula $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2^1/_2H_2O$.



Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and anti-pyretic. Its structural formula is shown at right. Its molecular weight is 151.17 and molecular formula $C_8H_9NO_2$.



Each tablet contains:
Hydrocodone* Bitartrate, USP ..... 5 mg
(***Warning: May be habit forming**)
Acetaminophen, USP ..... 500 mg

Also contains: Pregelatinized Starch, Anhydrous Lactose, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Stearic Acid and Purified Water.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β- hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS and USAGE

Hydrocodone and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone bitartrate and acetaminophen tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effects of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:
Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the overdosage section.

DRUG ABUSE and DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Tablets are classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE and ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

HOW SUPPLIED

Hydrocodone Bitartrate **(Warning: May be habit forming)** and Acetaminophen Tablets USP, 5 mg/ 500 mg are white, oval shaped tablets, scored on one side and debossed with HD 765 on the other side. They are packaged in bottle sizes of 100, 500 and 1000 tablets.

Store at controlled room temperature 15-30° C (59-86° F).

Dispense in a tight, light-resistant container with child-resistant closure.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by
HALSEY DRUG CO., INC.
Brooklyn, NY 11233-3599 U.S.A.

Revised 08/97
K.T.

08790765

HYDROCODONE BITARTRATE & ACETAMINOPHEN TABLETS, USP 5mg / 500mg

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040236

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-236

3. NAME AND ADDRESS OF APPLICANT
Halsey Drug Company, Inc.
1827 Pacific St.
Brooklyn, NY 11233

4. LEGAL BASIS FOR SUBMISSION
Certify to the best of their knowledge there are no patents that claim the listed drug product and referenced listed drug is not entitled to a period of marketing exclusivity.
Listed Product:
Knoll Pharmaceuticals, Inc. - Vicodin® 5 mg/500 mg
Knoll Pharmaceuticals, Inc. - Vicodin ES® 7.5 mg/750 mg

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
- 12/19/96 - Original.
- 3/27/97 - O/NC, independent application audit.
- 5/2/97 - Withdrawal of ANDA 40-238.
- 5/5/97 - Amendment, response to 2/14/97 letter.
- 5/7/97 - Amendment, response to 2/24/97 letter.
- 5/29/97 - O/NC, request for global review of ANDA 40-236 and 40-240, not granted 6/5/97.
- 8/8/97 - Response to 1st def. facsimile (chem. & labeling. Subject of this review.
- 8/28/97 - Response to 2nd def. facsimile (labeling). Subject of this review.
- 9/23/97 - Response to phone memo. Subject of this review.

FDA:
- 2/14/97 - Acknowledgment, address exclusivity.
- 2/24/97 - Letter requesting firm to withdraw ANDA 40-238 (5 mg/500 mg) and submit as amendment to ANDA 40-236.
- 6/17/97 - Bio. review, acceptable.
- 6/25/97 - Bio. letter, no further questions at this time.
- 7/31/97 - 1st def. facsimile (chem. & labeling).
- 8/25/97 - 2nd def. fascsimile (labeling).
- 9/22/97 - Phone memo, add *p*-aminophenol to finished product and stability.

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
R

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

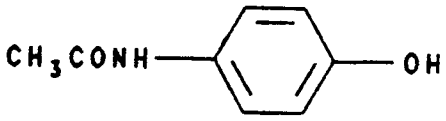
13. DOSAGE FORM
Tablet

14. POTENCY
5 mg/500 mg & 7.5 mg/750 mg

15. CHEMICAL NAME AND STRUCTURE

Acetaminophen USP

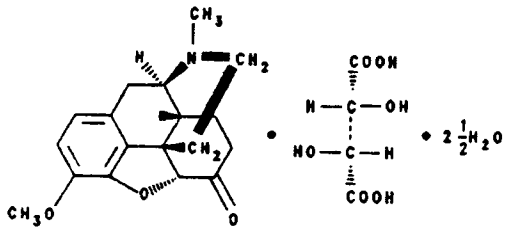
$C_8H_9NO_2$; M.W. = 151.16



4'-Hydroxyacetanilide. CAS [103-90-2]

Hydrocodone Bitartrate USP

$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$; M.W. = 494.50



4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). CAS [34195-34-1; 6190-38-1]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Method validation not needed, product is USP. DMFs, EER, labeling and Bio. are satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER:
Norman Gregory

DATE COMPLETED:
9/24/97 (chem.)
9/5/97 (labeling)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040236

BIOEQUIVALENCE REVIEW(S)

ANDA 40-236

JUN 25 1997

Halsey Drug Co., Inc.
Attention: George F.J. Scholes
1827 Pacific Street
Brooklyn NY 11233

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 5 mg/500 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

6/23/97

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 17 1997

Hydrocodone Bitartrate/
Acetaminophen
7.5mg/750mg , 5 mg/500 mg Tablets
ANDA #40-236
Reviewer: Jahnavi S. Kharidia
X:\wpfile\Biofinal\40236w.d96

Halsey Drug Company
245 Old Hook Road
Westwood, NJ 07675
Submission Date:
December 19, 1996
May 7, 1997
May 5, 1997

Review of Dissolution Data and Waiver Requests

Introduction:

Hydrocodone bitartrate is a phenanthrene-derivative opiate agonist that is used as an antitussive and analgesic agent. Acetaminophen is a synthetic non-opiate derivative of p-aminophenol which is used as analgesic and antipyretic. The combinations of Hydrocodone bitartrate/Acetaminophen are commercially available as 5 mg/500 mg capsules or 2.5 mg/500 mg, 5 mg/500 mg, 7.5 mg/500 mg and 7.5 mg/750 mg tablets.

Background:

On December 19, 1996, the firm submitted an ANDA# 40-236 for its Hydrocodone Bitartrate and Acetaminophen Tablets, 7.5 mg/750 mg. The firm then filed an ANDA# 40-238 for its Hydrocodone Bitartrate and Acetaminophen Tablets, 5 mg/500 mg. The OGD refused to file ANDA# 40-238 as per OGD Policy and Procedure Guide #20-90 (letter dated February 24, 1997) and requested the firm to withdraw the ANDA# 40-238 (letter dated May 2, 1997) and refile the appropriate information as an amendment under the companion ANDA# 40-236 for Hydrocodone Bitartrate and Acetaminophen Tablets, 7.5 mg/750 mg. The firm is now submitting an amendment (May 7, 1997) to ANDA# 40-236 for an additional strength of Hydrocodone and Acetaminophen Tablets (5 mg/500 mg).

Objective:

The firm is requesting waivers of *in vivo* bioequivalence requirements for its Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5 mg/750 mg and 5 mg/500mg. The firm has conducted dissolution testing on its test products comparing them to reference listed product, Knoll's Vicodin ES® 7.5 mg/750 mg Tablets and Knoll's Vicodin® 5 mg/500 mg Tablets, respectively.

Comments:

1. The drug product is classified AA in the list of the "Approved Drug Products With Therapeutic Equivalence Evaluations". Only an *in vitro* testing is required for bioequivalence.

2. The composition of test products are shown in Table 1.

Table 1: Comparative Formulation [Not to be released under FOI]

Strength	Ingredient	Reference Product mg/tablet	Test Product mg/tablet
7.5 mg/750 mg	Hydrocodone Bitartrate	7.5	7.5
	Acetaminophen	750	750
	Silicon Dioxide	(b)4 - Confidential Business	
	Magnesium Stearate		
	Stearic Acid		
	Croscarmellos		
	Starch, Corn		
	Povidone		
	Microcrystalline Cellulose		
	Lactose Anhydrous, NF		
5 mg/500 mg	Hydrocodone Bitartrate	5	5
	Acetaminophen	500	500
	Silicon Dioxide	(b)4 - Confidential Business	
	Magnesium Stearate		
	Calcium Phosphate, Dibasic,Dihydrate		
	Microcystalline Cellulose		
	Lactose Anhydrous, NF		
	Stearic Acid		
	Pregelatinized Starch		
	Croscarmellos		
	Povidone		
	Sodium Metabisulfite		

Source of reference product composition: COMIS Database

The potency was not listed in the COMIS database for some of the ingredients of the reference product.

3. The firm has submitted *in vitro* dissolution data for both ingredients using USP dissolution methodology. Dissolution data are summarized in Table 2.

Table 2 In Vitro Dissolution Testing

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

Method: USP XXIII **Apparatus:** 2 (Paddle), 50 RPM
No. Units: 12
Medium: 900 mL of phosphate buffer pH 5.8
Specifications: NLT (b)4 30 minutes for both ingredients
Reference Drug: Vicodin ES (Knoll) 7.5/750 mg Tablet
Vicodin (Knoll) 5/500 mg Tablet

II. Results of In Vitro Dissolution Testing: Hydrocodone Bitartrate

Sampling Times (Minutes)	Test Product Lot No. 960502 Strength: 7.5 mg/750			Vicodin ES Lot No. 10770555 Strength: 7.5 mg/750 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	103	(b)4 -	3.2	95	(b)4 -	4.3
20	103	nfiden	1.6	99	nfiden	3.5
30	103		1.2	99		2.4

Sampling Times (Minutes)	Test Product Lot No. 5M06 Strength: 5 mg/500 mg			Vicodin Lot No. 10760525 Strength: 5 mg/500 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	99	(b)4 -	2.2	92	(b)4 -	3.5
20	100	nfiden	2.2	93	nfident	4.0
30	100		2.3	96		4.6

III. Results of In Vitro Dissolution Testing: Acetaminophen

Sampling Times (Minutes)	Test Product Lot No. 960502 Strength: 7.5 mg/750			Vicodin ES Lot No. 10770555 Strength: 7.5 mg/750 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	99	(b)4 -	2.5	92	(b)4 -	5.0
20	102	nfiden	1.6	97	nfident	5.3
30	102		1.7	99		1.9

Sampling Times (Minutes)	Test Product Lot No. 5M06 Strength: 5 mg/500 mg			Vicodin Lot No. 10760525 Strength: 5 mg/500 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	98	(b)4 -	1.8	79	(b)4 -	8.5
20	99	nfiden	1.5	86	nfident	6.3
30	99		1.6	88		7.4

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The *in vitro* dissolution data have been found acceptable.

Recommendations:

1. The dissolution testing conducted by Halsey Drug Company on its Hydrocodone Bitartrate/Acetaminophen, 5 mg/500 and 7.5 mg/750 mg Tablets, lot #5M06 and lot #960502, respectively, is acceptable. Waivers of the in vivo bioequivalence study requirements are granted for the test products Hydrocodone Bitartrate/Acetaminophen, 5 mg/500 mg Tablets and 7.5 mg/750 mg Tablets, based on 21 CFR 320.22 (c).

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer pH 5.8, at 37 ° C using USP 23 apparatus 2 (paddle) at 50 rpm.
The test product should meet the following specifications:

   Not less than (b)4 of the labeled amount of both acetaminophen and hydrocodone bitartrate in the dosage form are dissolved in 30 minutes.

The firm should be informed of the above recommendations.

/S/

J. S. Kharidia
Division of Bioequivalence
Review Branch III

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FT INITIALED RMHATRE /S/ Date: 6/4/97
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